REMARKS

Claims 48, 4), 51-53, 55 and 58-59 are presently pending. Claims 50, 54, 56 and 57 have been canceled. These claims had been canceled in the remarks section in the Amendment After Final, but wer not formally canceled in the instructions to amend the claims. Applicant acknowledges the wi hdrawal of the double-patenting rejection and the new prior art rejection.

Rejection under 35 U.S.C. § 103(a)

Claims 48-5) are rejected under 35 U.S.C. § 103(a) as obvious over Eshhar *et al.*, *Proc. Nat'l Acad. S i. USA* 90: 720 (1993), WO 92/15322, Wagner *et al.*, *Biotech. Therap.* 3: 81 (1992), and "app licant's admission" at page 22 of the specification, in view of Hansen *et al.*, *Cancer* 71: 34 8 (1993) ("Hansen") and Losman *et al.*, *Int. J. Cancer* 56:580 (1994) ("Losman"). Appli ant respectfully traverses this rejection.

The Examin r has basically maintained her final rejection of claims 48-57 for the same reasons as set forth i n the previous Office Actions with the exception that she has added Losman as disclosing that W I2 is an anti-idiotypic antibody that is specific for MN-14, a Class III anti-CEA antibody. The Examiner maintains her position that Eshhar suggests the use of chimeric genes in adoptive ir mmunotherapy and that Eshhar and Wagner show that such chimeric genes can be used in dise ases caused by either tumors or infectious agent, and that this motivation comes from Eshhar. The Examiner takes the position that it would have been obvious to one of ordinary skill in the art to use the chimeric genes of Eshhar in adoptive immunotherapy to treat tumors and infectic us diseases. The Examiner further concludes that because of Escher's disclosure that man y adoptive immunotherapy techniques lack specificity, it also would have been obvious to ha ve the immunoglobulin encoding region of the chimeric gene encode an antibody that was specific for specific antigens on the surface of cells, i.e., TAA's. The Examiner further st tes that MN-14 is an art recognized antibody that binds to CEA and WI2 is an art recognized A 32 that mimics MN-14, and their use was suggested by the prior art.

However, t e examiner admits that the primary reference, Eshhar, does not teach or suggest a specific s owing that the chimeric gene can be used in adoptive immunotherapy, a specific showing th t the immunoglobulin can be used to recognize a TAA or a disease caused by an infectious a ent and the use of cytokines and/or administration of an anti-Id and the specific use of CE A. The examiner alleges that the secondary references or a combination thereof provide thes e missing teachings of Eshhar.

The pending claims are directed to a method of inducing a cellular immune response against a tumor that expresses CEA by administering transfected T cells and then at least one cytokine. The preser t invention specifically achieves this response in one of two ways:

Firstly, (1) t ansfected T cells are administered in an effective immunostimulatory amount and are proc uced by obtaining T cells from the patient and transfecting these T cells with an expressio . vector containing a DNA molecule encoding either a chimeric immunoglobulin/T c ell receptor or a chimeric immunoglobulin/CD3 protein, and wherein the immunoglobulin-en oding portion of the DNA molecule encodes the variable region of an antibody that binds with **a Class III anti-CEA antibody,** and further wherein the variable regions of the α and β polypeptide chains of said T cell receptor are replaced by the variable regions of this antibc dy; and then (2) at least one cytokine is administered.

Secondly, (1 transfected T cells are administered in an effective immunostimulatory amount and are pro luced by obtaining T cells from the patient and transfecting these T cells with an expressio n vector containing a DNA molecule encoding either a chimeric immunoglobulin/T ell receptor or a chimeric immunoglobulin/CD3 protein, and wherein the immunoglobulin-en oding portion of the DNA molecule encodes the variable region of **an anti-idiotypic anti body that recognizes a Class III anti-CEA antibody,** and further wherein the variabl e regions of the α and β polypeptide chains of said T cell receptor are replaced by the va iable regions of this antibody; and then (2) at least one cytokine is administered.

Applicant si bmits that it is not obvious to substitute the chimeric genes encoding the variable region of a Class III anti-CEA antibody or chimeric genes encoding the variable region of an anti-id otypic antibody that recognizes a Class III anti-CEA antibody in adoptive immunotherapy as disclosed in Exhhar. In this regard, there has been confusion regarding the classification of CE A and its related family members. See the attached website depiction by Motomu Kuroki (Appendix 1) showing the group of glycoproteins called CD66 antigens consisting of five d fferent glycoproteins with similar structures. Only an antibody to CD66e is a Class III anti-C EA antibody.

An exampl of this confusion is shown in Irvine (Appendix 2) that discloses anti-idiotypic antibodie (Ab2) generated against the murine monoclonal antibody COL-1 (Ab1), an allegedly CEA pecific antibody. But Applicant provides evidence that COL-1 is not a CEA specific antil ody as alleged in Irvine. Applicants provide a publication by Chen *et al.*, (Appendix 3), published at least three years after Irvine's publication, that shows that

COL-1 reacts with GM1a, a CEA family member present on granulocytes. Therefore, COL-1 is not an an i-CEA antibody. As shown in U.S. Patent No. 5,874,540 (Appendix 4), MN-14 is a mur ne Class III, anti-CEA antibody, which means that it is unreactive with meconium antigen by EIA and does not react with normal tissues (See U.S. Patent No. 5,874, 540, colum 5, lines 61-67). These publications by Irvine and Chen show that persons of ordinary skill in the art did not understand the importance of using a Class III anti-CEA specific antibody, so therefore why would a skilled person in the art even consider selecting the DNA of a Class III anti-CEA antibody to perform adoptive immunotherapy. Therefore, in view of confusion in the field, it would not be obvious to select and utilize a Class III anti-CEA antibody in the Eshhar method.

In regard to claims 58 and 59, that are specifically directed to MN-14 or humanized MN-14 as the Class III anti-CEA antibody and WI2 as the anti-idiotype antibody, respectively. Neither Hansen or Losman disclose the sequences of the MN-14 or WI2 antibodies. In this regards, applicant submits that the MN-14 and WI2 antibodies are proprietary antibodies of the assignee, Immunomedics, Inc., and was not made available to the public prior to the filing date of the priority document to which the present application claims priority. In support of the statement, applicant provides a declaration from Dr. Hans Hansen, the present inventor (Appendix 5) , and from the Dr. David M. Goldenberg, Chairman of the Board of applicants' assignee, Immunomedics, Inc. (Appendix 6), who declare that the murine antibody (MN-14) and the rat anti-idiotypic antibody (rWI2) were priority cell lines owned and possessed by Immunomedics, Inc. and that they were not available to the public prior to the priority date of the present application.

To be able to make a chimeric or humanized MN-14 or WI2 antibody, one of skill in the art would have to know the DNA sequences of the murine MN-14 and the rat WI2 antibodies and select the specific CDRs from the DNA sequences encoding the light chain and heavy chain variable regions or these regions. It is applicant's position, as discussed above, that the DNA sequences encoding these antibodies were not known prior to filing the priority application of the present application. Thus, it would not be possible to prepare the chimeric genes to transfect the T cells without possessing these DNA sequences. In regard to claims 58 and 59, the relevant issue is whether the DNA sequences of the specifically claimed antibodies are not known or available, which they were not.

Additionally, neither Eshhar or Wagner disclose administering a cytokine after infusing the transfected T cells rather the Examiner appears to be arguing that Eshhar suggests that a

cytokine, i.e., IL-2, is produced when the transfected T cells interact with the tumor. Applicant's specification on page[illegible] 25-30 discloses the preparation of the transfected T cells and the methods of using them to trea a patient. Particularly, page 30 lines 13-24 discloses methods to enhance the efficacy of adopti ve immunotherapy. The administration of cytokines is performed after the administration of trat sformed T cells to amplify the immune response.

The Examine r's arguments are directed to combining Eshhar and Wagner to make the transfected T cells but as applicant noted above, the method requires the subsequent administration of at l ast one cytokine. Applicant submits that none of the prior art publications used in this obvio sness rejection disclose administering a cytokine subsequent to the administration of the transfected T cells containing the DNA encoding the variable region of a Class III anti-CEA antbody or the DNA encoding the variable region of an anti-idiotypic antibody that recogn zes a Class III anti-CEA antibody and nor do any of these publications provide a rationale fc r doing so. In view of these arguments and amendments to the claims, it is requested that this rej ection of the pending claims be withdrawn.

In view of the above arguments, all of the claims are allowable and it is requested that all of the rejections be w ithdrawn.

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CONCLUSION

Applicant kir dly requests reconsider of the final rejection and entry of this amendment and response. The r esponse does not raise any new issues and reduces issues on apply. The features added to ind pendent claims 48 and 52 are present in the canceled dependent claims. In view of the foregoi ıg, it is respectfully urged that the present claims are in condition for allowance. An early notice to this effect is earnestly solicited. Should there be any questions regarding this applic ıtion, the Examiner is invited to contact the undersigned at the telephone number shown belov .

Respectfully submitted,

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Date

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